FRONTIERS

Scientists Must Challenge Today's Common Wisdom

BY JOSHUA LEDERBERG

The history of science is replete with successes achieved through repudiation of the common wisdom. In the following, I offer some unconventional and speculative challenges to how we think about some large problems in contemporary biology. Most are not new thoughts, but to my knowledge they have not been refuted. I know they are mostly wrong; but I am not sure all are. They will surely be addressed, and most solved, during the next century. If I could foretell exactly how, I would be wasting no time getting to work on them in the laboratory.

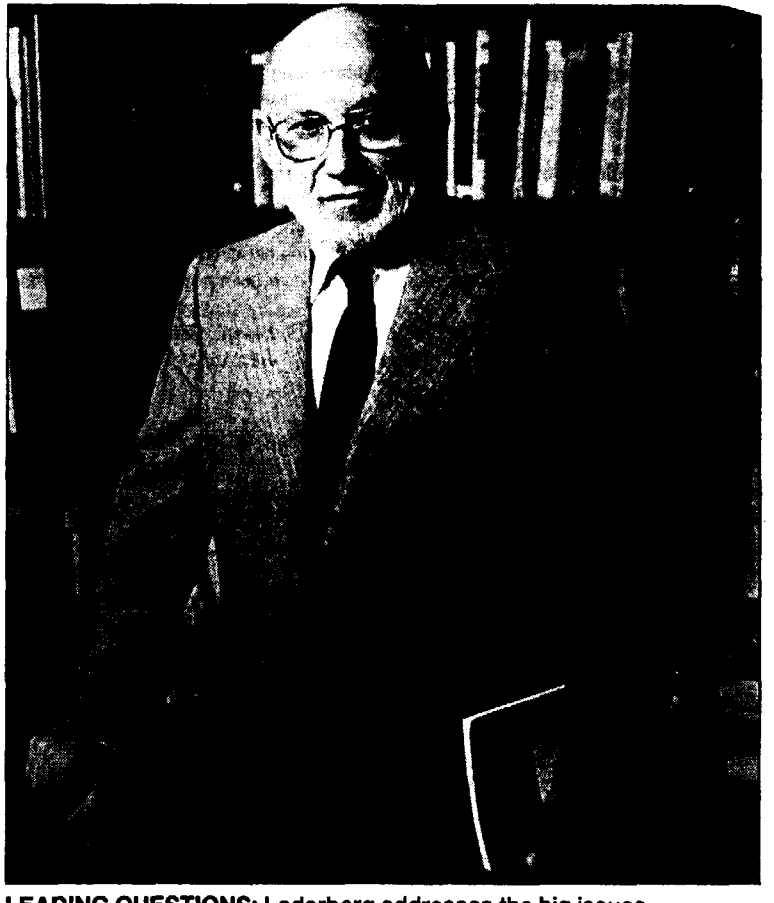
Frontiers are commentaries by pioneering researchers on breakthrough areas of science.

Eobiology. Conventional theory makes the origin of life a photochemical process of the early atmosphere of our own Earth. But the cosmic condensation necessarily involves preeminently light elements, including hydrogen, carbon, nitrogen, and oxygen. The aggregation of stars and planets is already an exercise in organic chemistry. Many large molecules have now been observed in space. Should we not look there for early chemical evolution, perhaps even of the rudiments of nucleic acids and proteins or their predecessors?

Exobiology. The cost of radio receivers and of computation may finally be reaching an asymptote that would justify some modest investment—if not now, in the next decade or two—in acquiring and processing potentially intelligent signals. We have no way to assess the probability of their occurrence. As to the solar system, the 1975 Viking mission gave a discouraging report on Mars; but it is wrong to foreclose the possibility of microhabitat refuges—especially at modest subsurface depth—perhaps from a more hospitable epoch in that planet's history. The thermal vents on our ocean floors offer an analogue of such habitats.

The Epigenetic Dilemma. The central model of cellular differentiation must reconcile (a) the orderly delimitation of gene expression in embryonic cell lineages, (b) the clonal inheritance of these self-sustaining differences, and (c) the apparent reversibility of these effects in some stages.

On account of (c), we usually assume the genetic uniformity of all somatic cells and, therefore, that epigenetic cell changes are epinucleic—that is, they do not alter the primary informational sequence of the DNA, but involve secondary structures or lateral attachments like methylation and histones. But, the dogma of genetic uniformity of somatic cells was overthrown with modern concepts of antibody formation. This is unlikely to be the only exploitation of nucleic diversification of somatic cells. Mechanisms of reversible nucleic differentiations are now known in prokaryotes.



LEADING QUESTIONS: Lederberg addresses the big issues.

Should we abandon the search for epinucleic explanations? I favor an eclectic perspective; but we have still to find a robust example and rationale of epinucleic transmission. We seek a consensually accepted experimental model, not just of modulation of gene expression, but also of its quasi-stable inheritance without nucleic alteration. The field might look for a Max Delbrück who would establish some discipline about the models to be pursued, as he did in plying phage T2 40 years ago.

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More attention also should be given to grossly obvious histological differentiation of nuclear and chromosomal structures: bands in polymorphs and dimples in monocytes must be epiphenomena of underlying chemical differentiation; and I will be rather surprised if they are not associated with fairly specific segments of DNA information and their current expression. The recent explorations of human fragile-X chromosomes show the value of correlating morphological and molecular-biological observations.

Aging. Here, too, we have yet to establish a consensus on what phenomenon we are investigating, on what would constitute an explanation. I suggest we use as a standard the difference in lifespan between human and mouse: Are there any cellular attributes that can be correlated with that outcome?

Cancer. The paradigm of the oncogene is properly taking hold, and I do not dispute it. Rather, I ask whether chemotherapy or radiotherapy can really be explained as solely responsible for eradication of all tumor cells. This seems very doubtful, and the collaboration of

endogenous biological defenses must be involved. If so, it has been mischievous to focus on modifiers like interferons or interleukins as sole therapeutic agents to be tested as single agents. They must be examined as adjuvants to cytocidal agents.

Heart Disease. The HDL/LDL (lipoprotein) ratio has been established as the best predictor of atherosclerosis. Almost no therapeutic research is founded on efforts to modify this ratio, which is certainly a question of differential gene expression under metabolic regulation in the liver.

Psychiatric Disease. Our *only* leads are (a) psychotropic drugs' mode of action and (b) genetic influences in disease. We are beginning to see important studies on DNA probes for polymorphisms linked to disease susceptibility. However, almost no one is looking at polymorphism in psychotropic drug metabolism, although there are many clinical hints of it. This would reflect the handling of endogenous metabolites.

Human Intelligence. Are we too wedded to the prewired switchboard model? There is abundant evidence for extensive cell migration during development. Could this continue throughout adult life and be part of learning? There is recent evidence of cell turnover, at least in song nuclei in birds. Is human cerebral function merely a numerical extrapolation of the neurobiology of lower mammals, or are there higher orders of differentiation of neuronal types in the human brain? If not, why is so much nucleic information uniquely expressed in the brain?

Physiology and Anatomy. That exercise influences muscle hypertrophy is an everyday observation. To understand it and other banalities at a molecular level could have great practical application: not just for Olympic competition, but for maintenance and rehabilitation of the heart and of that organ so uniquely vulnerable in the human, the intervertebral disk. To refer to "compensatory hypertrophy" of muscle or any other organ as a response to functional demand is hardly to explain its mechanism.

Toxicology. Toxic "side effects" are no longer incidental in the process of adoption of new drugs, pesticides, and other chemicals—they are the central issue. Toxicology must be elevated from a stepchild of pharmacology to a central position in the health sciences, as one of the most important applications of a fundamental molecular biological insight. Most of our expenditure on empirical toxicology is wasted; it would be better devoted to mechanistic analysis of toxic effects, especially the interaction of exogenous chemicals with oncogene mutation and expression.

The paradigm of comparative toxicology would seek a basic understanding of the similarities and differences of human responses to chemicals compared to other species. We can protect human health only by well-founded extrapolation from simpler models. Historically, toxic substances (metabolic inhibitors) had been central to the unraveling of metabolic pathways. The study of colchicine helped uncover tubulin; neurotoxins did the same for synaptic mechanisms. However, metabolic inhibitors have been displaced by more sophisticated tools of microanalysis, tracer methodology, genetic lesions for pathway analysis, and the direct isolation of enzymes. These have left a generation only dimly aware of that history.

Public Health and Epidemiology. We have no good alternative to the blind clinical trial—but this is devoid of mechanistic content. Therefore, it tests only the narrowest of hypotheses: the efficacy of the specific treatment, conducted precisely according to the protocol. Its conclusions could be quite misleading about the most minute variations, unless a sensitivity criterion can be established.

Parasitology. When I started compiling this list a decade ago, I felt it proper to press not only the humanistic importance but the scientific excitement that would attach to intensified research on protozoan and helminthic parasites. The World Health Organization's Tropical Disease Research initiative, with financial support from many foundations, is now a global scientific network devoted to these problems. The effort still needs much more support, especially from governments. There is no doubt that the field will be one of the most challenging and effective for the application of the modern tools of molecular biology.

Looking backward into the future, we are not so arrogant as to prophecy the scope and provenance of the global scientific effort of a full century. Compare 1887 with 1987, and recall how science grows exponentially! As to content, the surest prediction is that many of our firmest beliefs will be seen as crude approximations, evoking nostalgia, amusement, derision, or—worst of all—indifference, in the hindsight of 2087. S

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The foregoing has been excerpted from "The Second Century of Louis Pasteur: A Global Agenda for Biomedical Research," *his keynote address delivered on October 5, 1987, on the occasion of the centenary celebration of the Pasteur Institute in Paris.*